Fc-GGGGG-IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 34);

A4

and physiologically acceptable salts thereof.

REMARKS

The Applicants' representative would like to thank the Examiner for time taken and courtesy extended on March 27, 2002 to discuss and clarify outstanding issues in the application. Should the Examiner have any questions regarding this Response, he is encouraged to contact the undersigned.

I. Status of the Claims

Claims 1-34 are currently pending in the instant case and claim 24 is under examination. Claims 1-23 and 25-34 are withdrawn from further consideration under 37 C.F.R. 1.142(b). Claim 24 stands rejected under 35 U.S. C. §112, second paragraph.

II. The Amendments

The specification has been amended to correct a typographical error present in the sentence under the title "THROMBOPOIETIC COMPOUNDS," beginning at page 1, line 3. Specifically, the Provisional Application Serial No. to which priority is being claimed is change from 06/105,384 to the correct number 60/105,384. The specification has also been amended to correct a typographical error present in the paragraph under "FIELD OF THE INVENTION", beginning at page 1, line 8. Specifically, "of production" is changed to "production of" to reflect correct idiomatic English.

The claims have been amended to correct typographical errors in claims 16 and 24. As evidenced by the specification and the sequence listing, the SEQ ID numbering in claims 16 and 24 is off by one number. Therefore, claim 16 should be drawn to SEQ ID NOs:10-21 rather than SEQ ID NOs:9-20. Likewise, claim 24 should be drawn to SEQ ID NOs:22-34 rather than 21-33. The claims have been amended accordingly.

Applicants direct the Examiner's attention to the species election made in response to the restriction requirement dated March 26, 2001. Applicants originally elected with traverse claims 1-16, 24 and 27 (Group I) for continued prosecution and further elected the species designated as SEQ ID NO:33. As indicated by the amendment to claim 24 above, the species originally elected (SEQ ID NO:33) is now designated SEQ ID NO:34.

Applicants' representative verifies that no new matter is added by the above amendments. For the Examiner's convenience, Applicants have attached, as

Appendix A, a clean copy of all the claims pending upon entry of the present amendment. In addition, Applicants have attached Appendix B labeled "Version with Markings to Show Changes Made." Applicants respectfully request entry of the indicated amendments in the instant Application prior to further substantive examination.

As amended, the pending claims remain drawn to compounds having thrombopoietic activity that may be used to increase production of platelets or platelet precursors (e.g., megakaryocytes) in a mammal.

III. Priority

On page 3 of the outstanding Office Action, the Examiner notes that priority to the provisional application 60/105,348 has not been granted. According to the Examiner, the Office is unable to determine whether the elected invention was actually adequately disclosed in the provisional application because neither a Sequence Listing nor a computer readable form thereof was filed with the provisional application.

The Applicants in response assert that the provisional application as filed contains the same claims as the instant utility application and therefore discloses every compound found in the utility application including the elected species. Applicants further direct the Examiner to claim 24 of the provisional application wherein the elected species, Fc-GGGGG-IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA, is clearly disclosed.

Contrary to the Examiner's allegation, the elected nucleotide sequence of claim 24 designated SEQ ID NO:34 (after entry of this Amendment correcting SEQ ID NOs) is adequately disclosed in the provisional application and priority of the instant utility application should be granted to the claimed provisional application, 60/105,348, filed on October 23, 1998.

IV. The Information Disclosure Citation (PTO-1449)

On page 4 of the Office Action, the Examiner asserts deficiencies in the Information Disclosure Citation (i.e., PTO-1449) as filed. According to the Examiner, the references will not be considered by the Office "because (1) for the US patents, names of inventors, class and subclass on the PTO-1449 are not filled in and (2) for the non-patent reference(s), copies are not provided to the Office."

Under 37 C.F.R. 198 regarding the content required in an Information Disclosure Citation, section (b)(1) states, "Each U.S. patent listed in an information disclosure statement must be identified by inventor, patent number, and issue date." Accordingly, the Applicants submit herewith, a substitute PTO-1449 form, having the required contents. With regard to the Examiner's assertion that copies of the non-patent

references were not provided to the Office, the Applicants disagree. A postcard forwarded to the Patent Office with the application indicated that 86 references were submitted, and the date stamped by the Patent Office on this return postcard (Exhibit A) indicates receipt of all references by the Patent Office on October 22, 1999. However, in order to expedite prosecution, the Applicants resubmit copies of the non-patent references herewith.

V. The Objection to the Specification

The Examiner objected to the specification in response to the Draftperson's objection to the drawings. Under 35 U.S.C. §113, drawings are required upon filing only where such drawings are necessary for the understanding of the invention. The Applicants respectfully submit that formal drawings are not necessary for the understanding of the invention, rather, only a Sequence Listing is necessary. Accordingly, the Applicants will submit an appropriate amendment to correct the informalities in the drawings upon indication of allowance of the claims.

VI. Patentability Arguments

A. The rejection of claim 24 under 35 U.S.C. §112, second paragraph should be withdrawn.

Claim 24 was rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. Specifically, the Examiner rejected claim 24 because it is dependent from non-elected claim 1 and the metes and bounds of claim 24 is thus unclear.

Applicants note that claim 24 should have depended from claim 17 which is obvious because (i) the Fc moieties are described in claim 17 and not in claim 1 and, (ii) the presence of the Fc moiety is found in all compounds recited in claim 24. In accordance with the Examiner's suggestion, claim 24 has been amended to remove its dependency. Therefore, the rejection to claim 24 under §112, second paragraph, may properly be withdrawn.

SUMMARY

In view of the amendments and remarks made herein, the Applicants believe that claim 24 is in condition for allowance and request notification of the same.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

By _____

Joseph A. Williams, Jr. (Reg. No. 38,659)
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402
(312) 474-6300

March 28, 2002

APPENDIX A

Currently Pending Claims

1. A compound that binds to an mpl receptor comprising the structure

TMP_1-$(L_1)_n$-TMP_2

wherein TMP_1 and TMP_2 are each independently selected from the group of core compounds comprising the structure:

X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10},

wherein,

X_2 is selected from the group consisting of Glu, Asp, Lys, and Val;
X_3 is selected from the group consisting of Gly and Ala;
X_4 is Pro;
X_5 is selected from the group consisting of Thr and Ser;
X_6 is selected from the group consisting of Leu, Ile, Val, Ala, and Phe;
X_7 is selected from the group consisting of Arg and Lys;
X_8 is selected from the group consisting of Gln, Asn, and Glu;
X_9 is selected from the group consisting of Trp, Tyr, and Phe;
X_{10} is selected from the group consisting of Leu, Ile, Val, Ala, Phe, Met, and Lys;
L_1 is a linker; and
n is 0 or 1;

and physiologically acceptable salts thereof.

2. The compound according to Claim 1 wherein said TMP_1 and TMP_2 are independently selected form the group consisting of:

X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11};
X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12};
X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13};
X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14};
X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10};
X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11};
X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12};
X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}; and
X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14},

wherein X_2 - X_{10} are as defined;

X_1 is selected from the group consisting of Ile, Ala, Val, Leu, Ser, and Arg;

X_{11} is selected from the group consisting of Ala, Ile, Val, Leu, Phe, Ser, Thr, Lys, His, and Glu;

X_{12} is selected from the group consisting of Ala, Ile, Val, Leu, Phe, Gly, Ser, and Gln;

X_{13} is selected from the group consisting of Arg, Lys, Thr, Val, Asn, Gln, and Gly; and

X_{14} is selected from the group consisting of Ala, Ile, Val, Leu, Phe, Thr, Arg, Glu, and Gly.

3. The compound according to Claim 1 wherein said TMP_1 and/or TMP_2 are derivatized as set forth in one or more of the following:

one or more of the peptidyl [-C(O)NR-] linkages (bonds) have been replaced by a non-peptidyl linkage such as a -CH_2-carbamate linkage [-CH_2-OC(O)NR-]; a phosphonate linkage; a -CH_2-sulfonamide [-CH_2-$S(O)_2$NR-] linkage; a urea [-NHC(O)NH-] linkage; a -CH_2-secondary amine linkage; or an alkylated peptidyl linkage [-C(O)NR^6- where R^6 is lower alkyl];

the N-terminus is a -NRR^1 group; to a -NRC(O)R group; to a -NRC(O)OR group; to a -$NRS(O)_2$R group; to a -NHC(O)NHR group where R and R^1 are hydrogen and lower alkyl with the proviso that R and R^1 are not both hydrogen; to a succinimide group; to a benzyloxycarbonyl-NH- (CBZ-NH-) group; or to a benzyloxycarbonyl-NH- group having from 1 to 3 substituents on the phenyl ring selected from the group consisting of lower alkyl, lower alkoxy, chloro, and bromo;

the C terminus is -$C(O)R^2$ where R^2 is selected from the group consisting of lower alkoxy and -NR^3R^4 where R^3 and R^4 are independently selected from the group consisting of hydrogen and lower alkyl.

4. The compound according to Claim 1 wherein all of the amino acids have a D configuration.

5. The compound according to Claim 1 wherein at least one of the amino acids has a D configuration.

6. The compound according to Claim 1 which is cyclic.

7. The compound according to Claim 1 wherein TMP_1 and TMP_2 are each

Ile-Glu-Gly-Pro-Thr-Leu-Arg-Gln-Trp-Leu-Ala-Ala-Arg-Ala. (SEQ ID NO: 1)

8. The compound according to Claim 1 wherein L_1 comprises a peptide.

9. The compound according to Claim 8 wherein L_1 comprises Y_n, wherein Y is a naturally-occurring amino acid or a stereoisomer thereof and n is 1 through 20.

10. The compound according to Claim 8 wherein L_1 comprises $(Gly)_n$, wherein n is 1 through 20, and when n is greater than 1, up to half of the Gly residues may be substituted by another amino acid selected from the remaining 19 natural amino acids or a stereoisomer thereof.

11. The compound according to Claim 8 wherein L_1 is selected from the group consisting of

$(Gly)_3Lys(Gly)_4$ (SEQ ID NO: 6);
$(Gly)_3AsnGlySer(Gly)_2$ (SEQ ID NO: 7);
$(Gly)_3Cys(Gly)_4$ (SEQ ID NO: 8); and
GlyProAsnGly (SEQ ID NO: 9).

12. The compound according to Claim 8 wherein L_1 comprises a Cys residue.

13. A dimer of the compound according to Claim 12.

14. The dimer according to claim 13 which is

TMP_1-Gly_3-Cys-Gly_4-TMP_2

|

TMP_1-Gly_3-Cys-Gly_4-TMP_2.

15. The compound according to Claim 1 wherein L_1 comprises $(CH_2)_n$, wherein n is 1 through 20.

16. The compound according to Claim 1, which is selected from the group consisting of

IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA (SEQ. ID NO: 10)

IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (cyclic)
(SEQ. ID NO: 11)

IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (linear)
(SEQ. ID NO: 12)

IEGPTLRQALAARA-GGGGGGGG-IEGPTLRQALAARA (SEQ. ID NO: 13)

IEGPTLRQWLAARA-GGGKGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 14)

IEGPTLRQWLAARA-GGGK(BrAc)GGGG-IEGPTLRQWLAARA
(SEQ. ID NO: 15)

IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 16)

IEGPTLRQWLAARA-GGGK(PEG)GGGG-IEGPTLRQWLAARA
(SEQ. ID NO: 17)

IEGPTLRQWLAARA-GGGC(PEG)GGGG-IEGPTLRQWLAARA
(SEQ. ID NO: 18)

IEGPTLRQWLAARA-GGGNGSGG-IEGPTLRQWLAARA (SEQ. ID NO: 19)

IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA

|

IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 20);

IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 21).

24. A compound that binds to an mpl receptor, which is selected from the group consisting of

Fc-IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA (SEQ. ID NO: 22)

Fc-IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA-Fc (SEQ. ID NO: 23)

IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA-Fc
(SEQ. ID NO: 24)

Fc-GG-IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA (SEQ. ID NO: 25)

Fc-IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA
(SEQ. ID NO: 26)

Fc-IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (cyclic)
(SEQ. ID NO: 27)

Fc-IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (linear)
(SEQ. ID NO: 28)

Fc-IEGPTLRQALAARA-GGGGGGGG-IEGPTLRQALAARA (SEQ. ID NO: 29)

Fc-IEGPTLRQWLAARA-GGGKGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 30)

Fc-IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 31)

Fc-IEGPTLRQWLAARA-GGGNGSGG-IEGPTLRQWLAARA (SEQ. ID NO: 32)

Fc-IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA

Fc-IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 33)

Fc-GGGGG-IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA
(SEQ. ID NO: 34);

and physiologically acceptable salts thereof.

27. A pharmaceutical composition comprising a compound according to Claim 1 in admixture with a pharmaceutically acceptable carrier thereof.

Appendix B

Version with Markings to Show Changes Made

I. Amendments in the Specification:

Page 1, line 3:
--This application claims priority of U.S. Provisional Application Serial No. [06/105,348] 60/105,348 filed October 23, 1998.--

Page 1, line 8:
--The compounds of the invention may be used to increase [of production] production of platelets or platelet precursors (e.g., megakaryocytes) in a mammal.--

II. Amendments in the Claims:

16. (Amended) The compound according to Claim 1, which is selected from the group consisting of

IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA (SEQ. ID NO: [9]10)

IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (cyclic)
(SEQ. ID NO: [10]11)

IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (linear)
(SEQ. ID NO: [11]12)

IEGPTLRQALAARA-GGGGGGGG-IEGPTLRQALAARA (SEQ. ID NO: [12]13)

IEGPTLRQWLAARA-GGGKGGGG-IEGPTLRQWLAARA (SEQ. ID NO: [13]14)

IEGPTLRQWLAARA-GGGK(BrAc)GGGG-IEGPTLRQWLAARA
(SEQ. ID NO: [14]15)

IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: [15]16)

IEGPTLRQWLAARA-GGGK(PEG)GGGG-IEGPTLRQWLAARA
(SEQ. ID NO: [16]17)

IEGPTLRQWLAARA-GGGC(PEG)GGGG-IEGPTLRQWLAARA
(SEQ. ID NO: [17]18)

IEGPTLRQWLAARA-GGGNGSGG-IEGPTLRQWLAARA (SEQ. ID NO: [18]19)

IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA
|
IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: [19]20);

IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA (SEQ. ID NO: [20]21).

24. (Amended) A compound that binds to an mpl receptor, which is selected from the group consisting of

Fc-IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA (SEQ. ID NO: [21]22)

Fc-IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA-Fc (SEQ. ID NO: [22]23)

IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA-Fc (SEQ. ID NO: [23]24)

Fc-GG-IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA (SEQ. ID NO: [24]25)

Fc-IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA (SEQ. ID NO: [25]26)

Fc-IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (cyclic) (SEQ. ID NO: [26]27)

Fc-IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (linear) (SEQ. ID NO: [27]28)

Fc-IEGPTLRQALAARA-GGGGGGGG-IEGPTLRQALAARA (SEQ. ID NO: [28]29)

Fc-IEGPTLRQWLAARA-GGGKGGGG-IEGPTLRQWLAARA (SEQ. ID NO: [29]30)

Fc-IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO:[30]31)

Fc-IEGPTLRQWLAARA-GGGNGSGG-IEGPTLRQWLAARA (SEQ. ID NO: [31]32)

Fc-IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA

Fc-IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: [32]33)

Fc-GGGGG-IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA (SEQ. ID NO: [33]34);

and physiologically acceptable salts thereof.

Exhibit A

01017/36263 102299-08

The Patent Office is hereby requested to acknowledge receipt of the following papers by stamping and returning this card.

WITH SERIAL NO. AND FILING DATE
Liu et al.
Thrombopoietic Compounds
Patent Application Transmittal (and copy)
Title Page, Specification 57 pages. Claims 9 pages,
Abstract, Drawings 6 pages, Sequence Listing 17 Pages
Executed Declaration; Assignment Transmittal;
IDS w/1449 Form; 18 US; 10 PCT; 58 Others
1.821(f) Statement & Diskette; Fee$1254.00 #
w/Certificate of Mailing by U.S.P.S. Express Mail
dated Oct. 22, 1999. Label No.:EM362734115US